

Epidemiologic Studies of Cancer Risk Following Diagnostic Radiation or Radiotherapy for Benign Diseases

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Natural Sources :

Environmental

Cosmic Radiation

Terrestrial Radiation

Internal Radioactive
Isotopes

Manmade Sources :

Environmental

Technologically Enhanced
Global Fallout

Nuclear Power

Medical

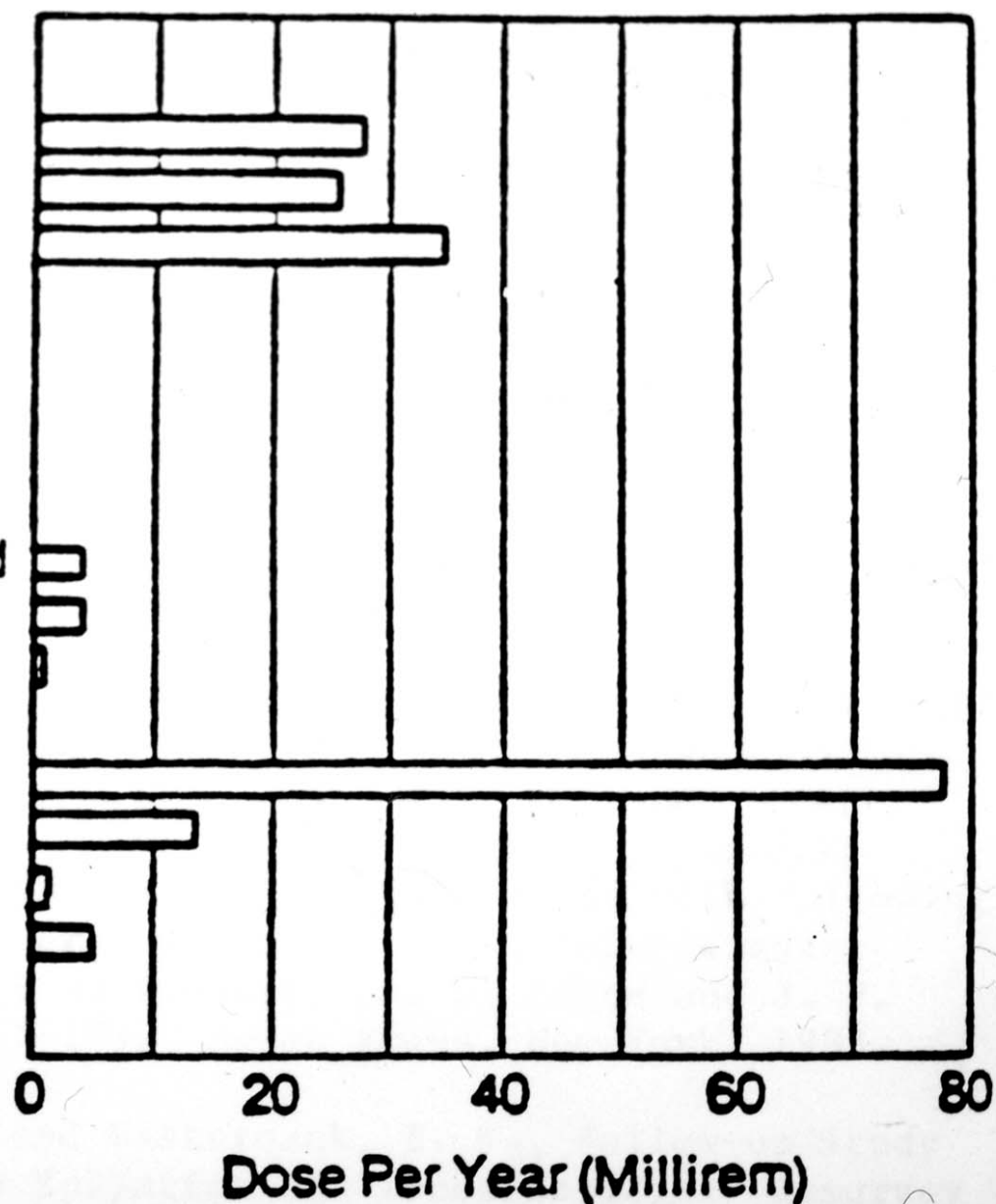
Diagnostic

Radiopharmaceuticals

Occupational

Consumer Products

and Miscellaneous



Estimated Organ Doses from Selected Diagnostic Procedures

(de Gonzalez, *Lancet* 363:345, 2004)

Procedure	Organ	Dose (mGy)
Chest x-ray	Lung	0.07
Mammography (1-view)	Breast	2.0
Coronary angiography	Lung	38
Barium enema	Bladder	14
Lumbar spine	Bladder, Colon	~2.4
CT: abdomen	Stomach	22
CT: thoracic spine	Breast	28

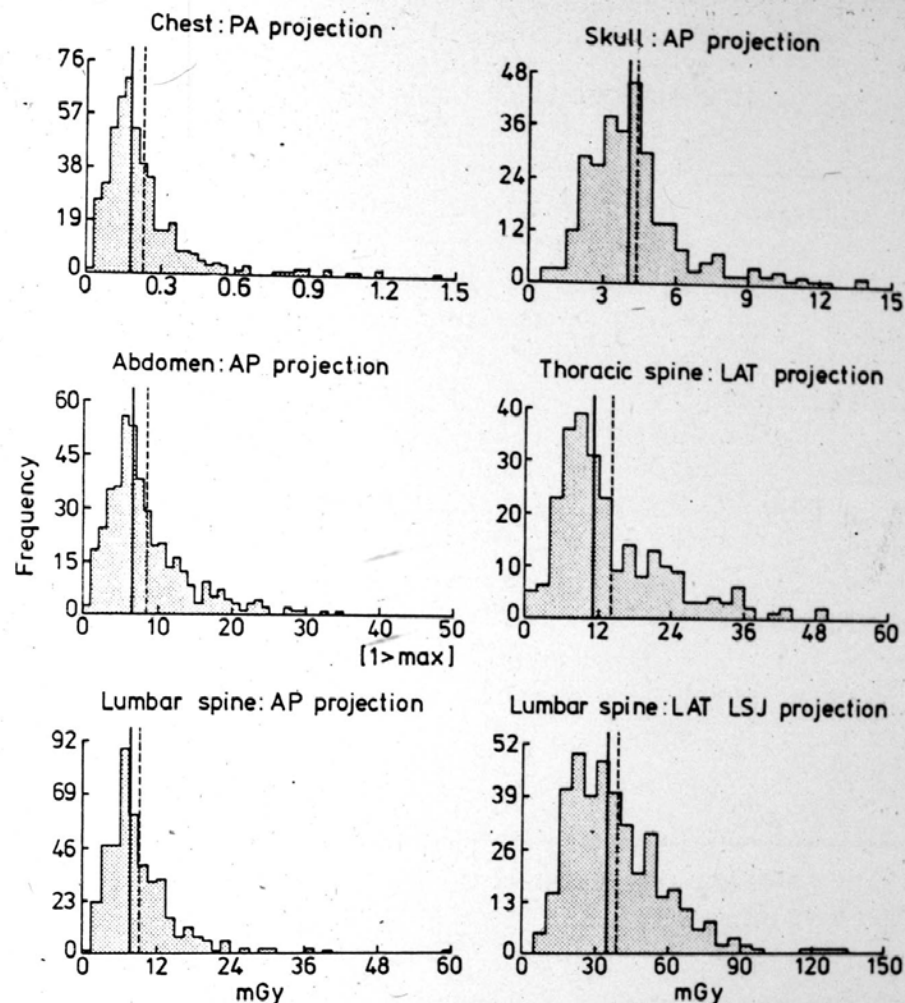
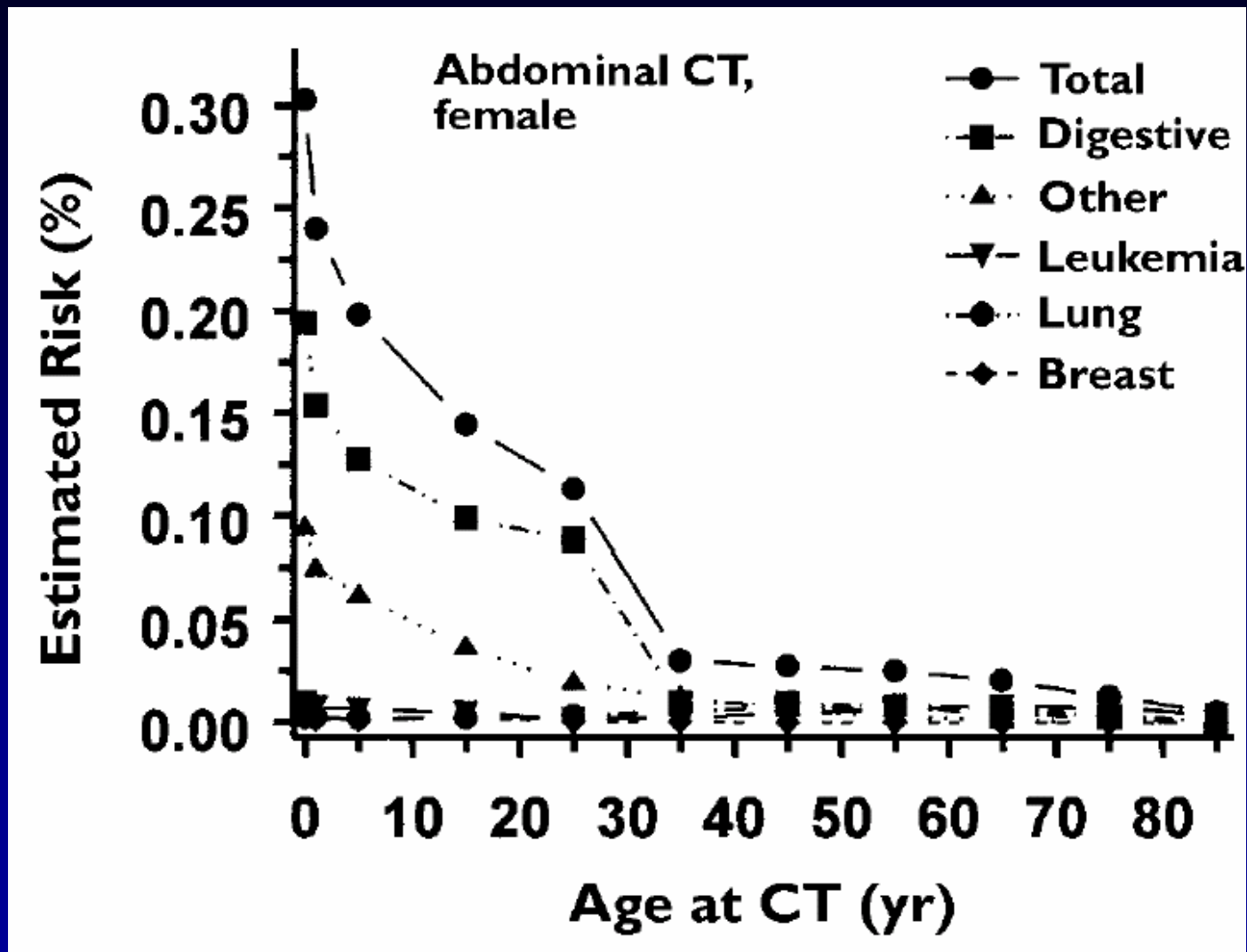


FIG. 3.

Histograms of measurements of entrance skin dose per radiograph during six common X-ray examinations for a random sample of adult patients in England. Means and medians of distributions are indicated by dotted lines and continuous lines, respectively. The maximum value observed during AP projection of the abdomen of 62.4 mGy has been omitted from the third histogram.

Radiation Doses from CT

Organ Doses from Abdominal CT by Age



Brenner et al, AJR 176:293, 2001.

Radiation Dose Limitation: Problem with CT Scans

- If patient overexposed, computerized image will automatically adjust for it, unlike film.
- CT machines had one body-size setting, so children were being overexposed.
- CT tech may expose larger area to be sure desired features are in image. Radiologist won't know about it.
- Cine mode will take multiple images & tech will select the 1 that is best, unbeknown to radiologist.
- Result: CT is 11% of procedures, but gives 70% of patient dose.

(Per Fred Mettler, Univ. New Mexico, 2002)

X-ray Treatment for Tinea Capitis

Shielding for Tinea Capitis X-irradiation



Radiotherapy for Tinea Capitis

Typical radiologic parameters	5 fields, 300-380 R/field, 100 kVp unfiltered, HVL .75mm Al
Dose to scalp	3.3-6 Gy
Dose at margin of scalp	2.5 Gy
Dose to face and neck	0.1-0.5 Gy
Dose to brain	1.7 Gy to cerebrum 0.7 Gy to cerebellum
Dose to thyroid gland	0.06 Gy

Characteristics of the Irradiated and Unirradiated Tinea Capitis Study Subjects

	<u>Irradiated</u> (N=2,224)	<u>Unirradiated</u> (N=1,380)
Median age (y) at Tinea Tx (90% range)	7.8 (3.9-12.1)	7.4 (2.4-12.7)
% Female	12.8	21.4
% African-American	23.6	25.0
Median years of follow-up (90% range)	39.3 (15.1-46.9)	38.5 (14.9-46.8)
% with follow-up at last survey or dead	88.1	84.4

Tinea X-ray Treatment: Skin Cancer

Principal Studies of Ionizing Radiation and Skin Cancer Risk

	A-bomb ^A	Israeli Tinea ^B	NYC Tinea ^C
# irradiated	48, 441	10,834	2,224
Length follow-up (y)	30	25	39
Mean dose (Sv)	0.33	6.8	4.8
Obs/Exp. BCC	54 / 34	41 / 8.4	125 / 35
BCC: RR at 1 Sv	2.8 (1.8-4.3)	1.7 (1.3-2.4)	1.6 (1.3-2.0)

^A Ron E, et al (1998). Cancer Caus. Cont. **9**: 393-401.

^B Ron E, et al (1991). Radiat. Res. **125**: 318-325.

^C Shore R, et al (2002). Radiat. Res. **157**: 410-18.

Pathological Characteristics of Radiation-Induced Skin Cancer of the Head/Neck

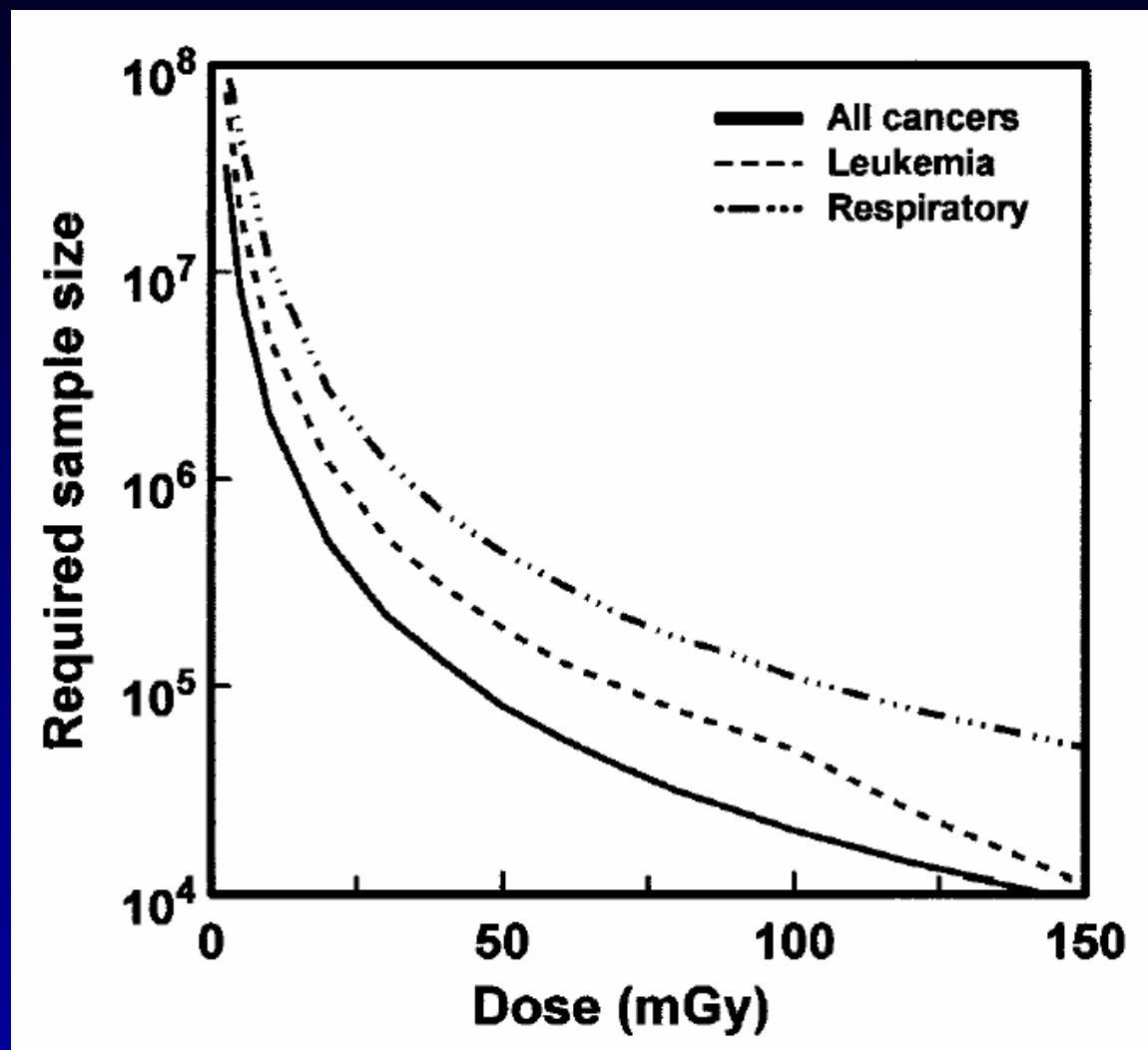
	<u>Irradiated : Control</u>
Basal cell	128/38 : 21/21
Squamous cell	7 : 0
Malignant melanoma	0 : 0

Multiple Skin Cancers in Irradiated Group

# Skin Cancers	# Cases
1	79
2	17
3-4	16
5-9	9
10-30	7
Total cases	128
Total skin cancers	340
Probability of additional skin Ca = 19%/y/person	

Epidemiologic Aspects of Radiation Studies

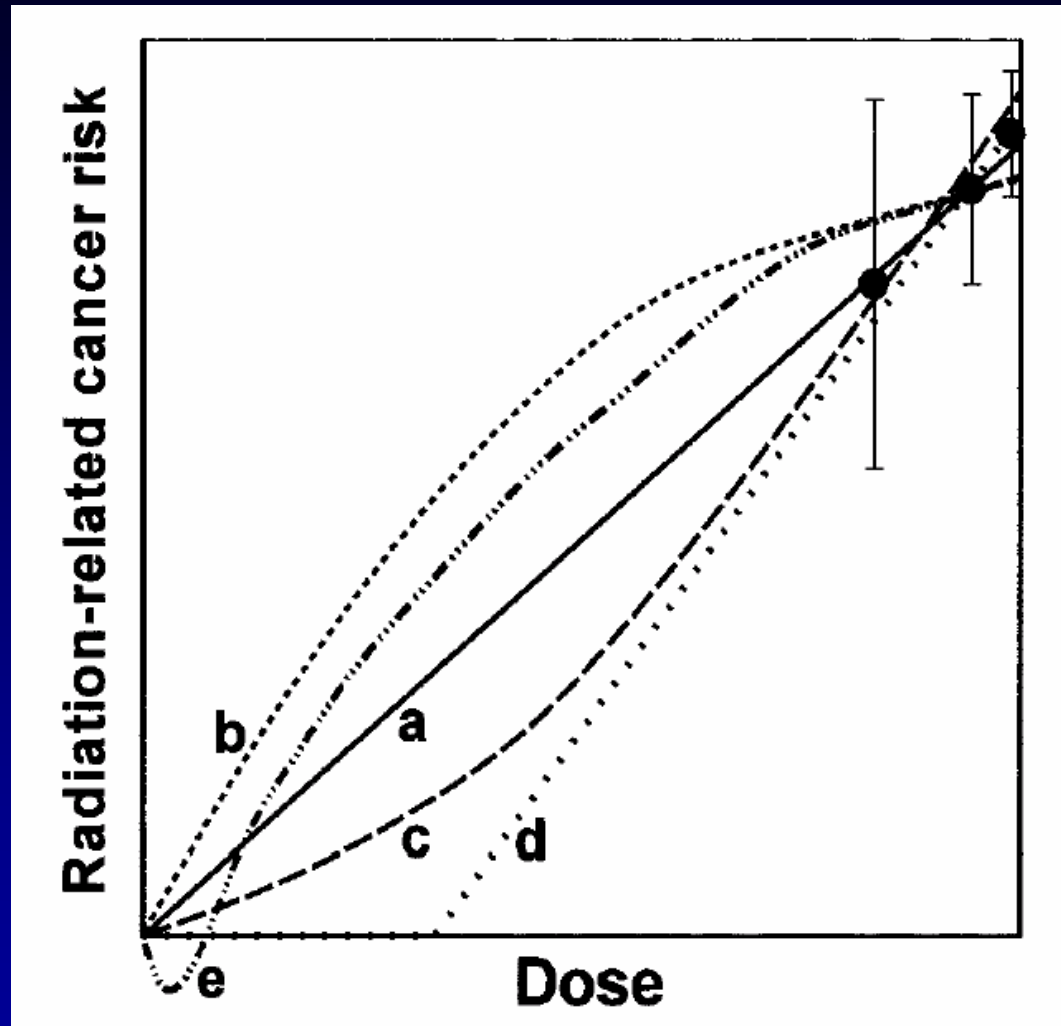
Sample Size Needed to Study Various Doses



Brenner et al, PNAS 100:13762, 2003.

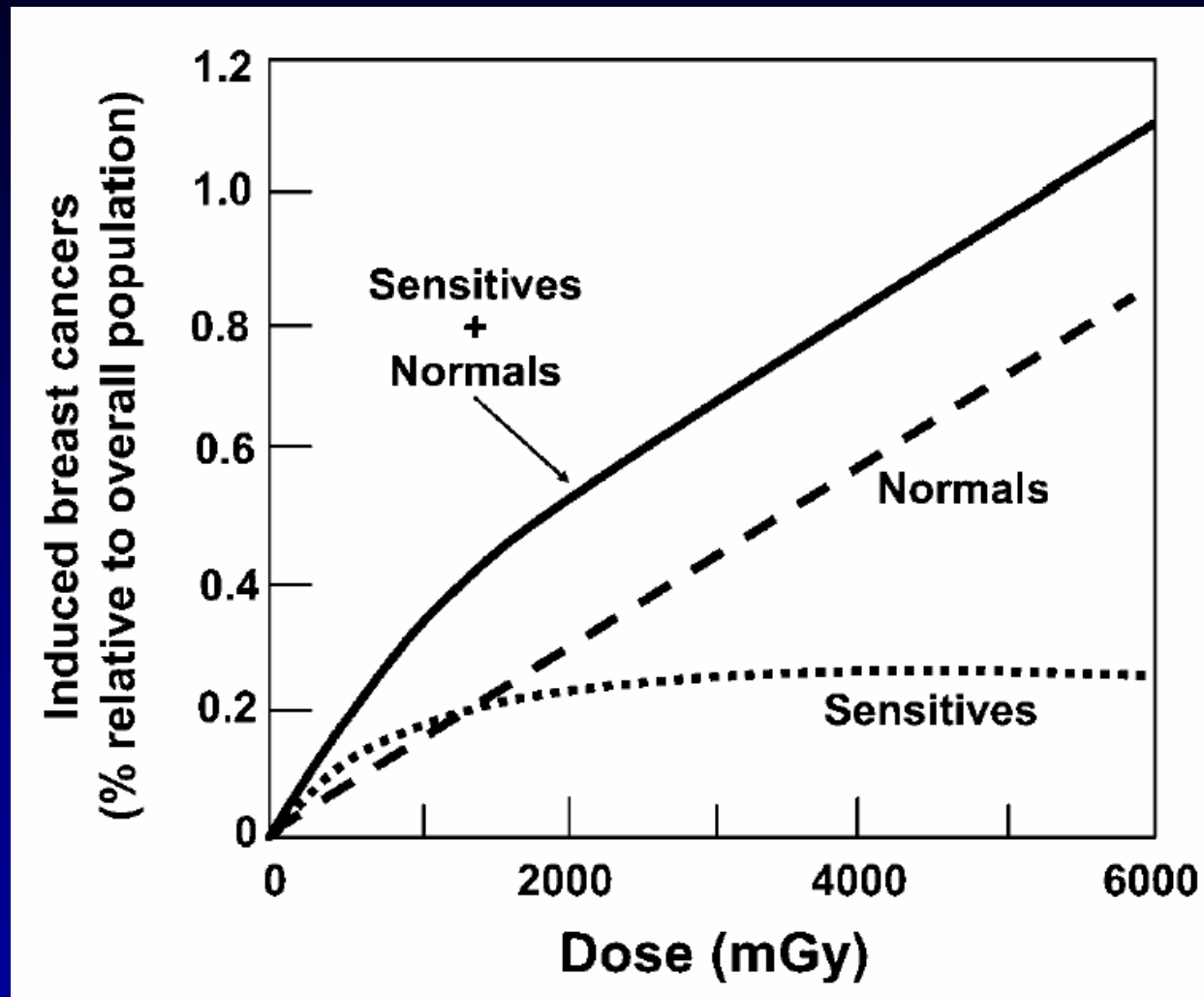
Dose-Response Analyses

Possible Dose-Response Shapes

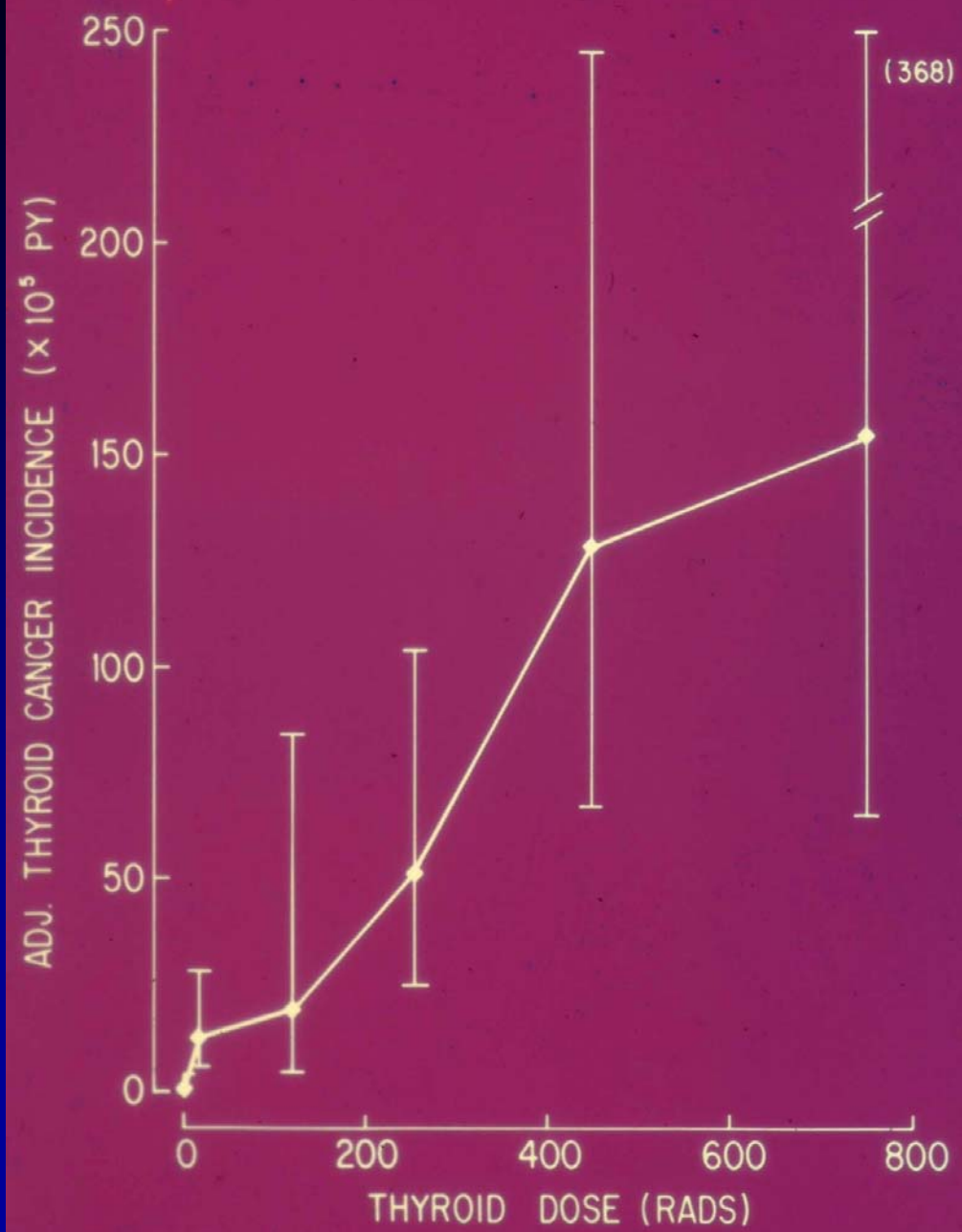


Brenner et al, PNAS 100:13763, 2003.

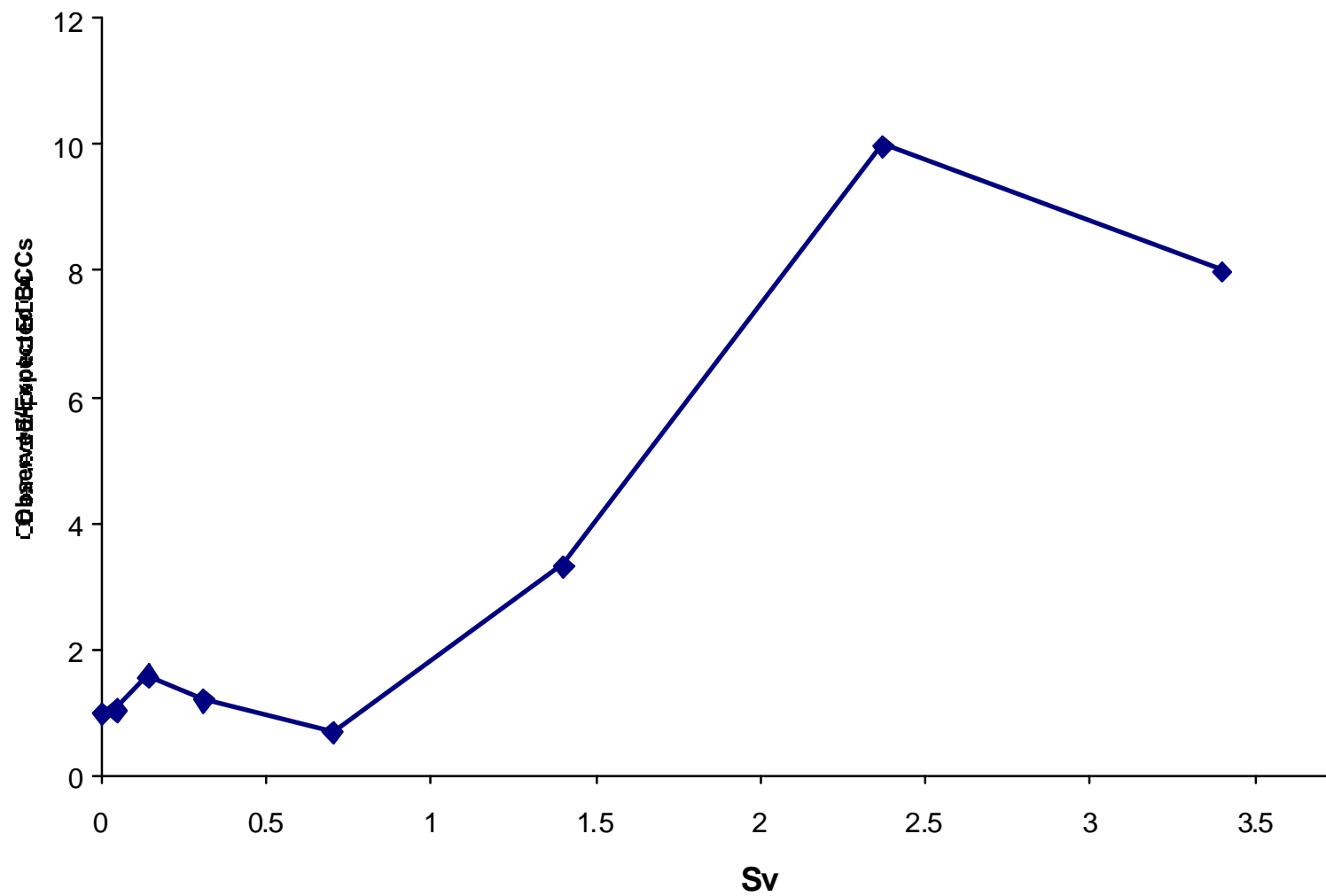
Scenario with a Subpopulation of Highly Sensitive Persons



Brenner et al, PNAS 100:13764, 2003.

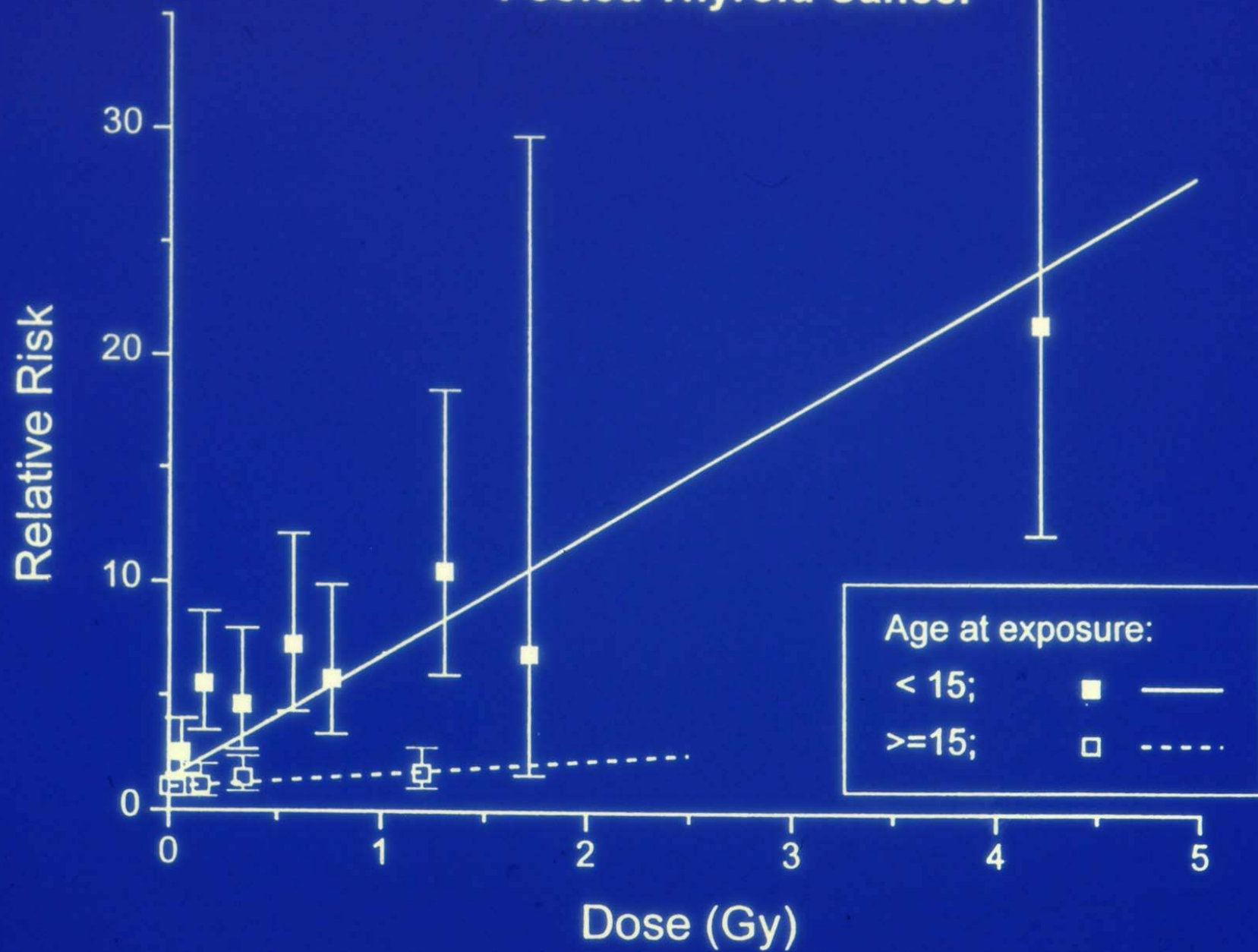


BCC by Dose (A-bomb survivors)

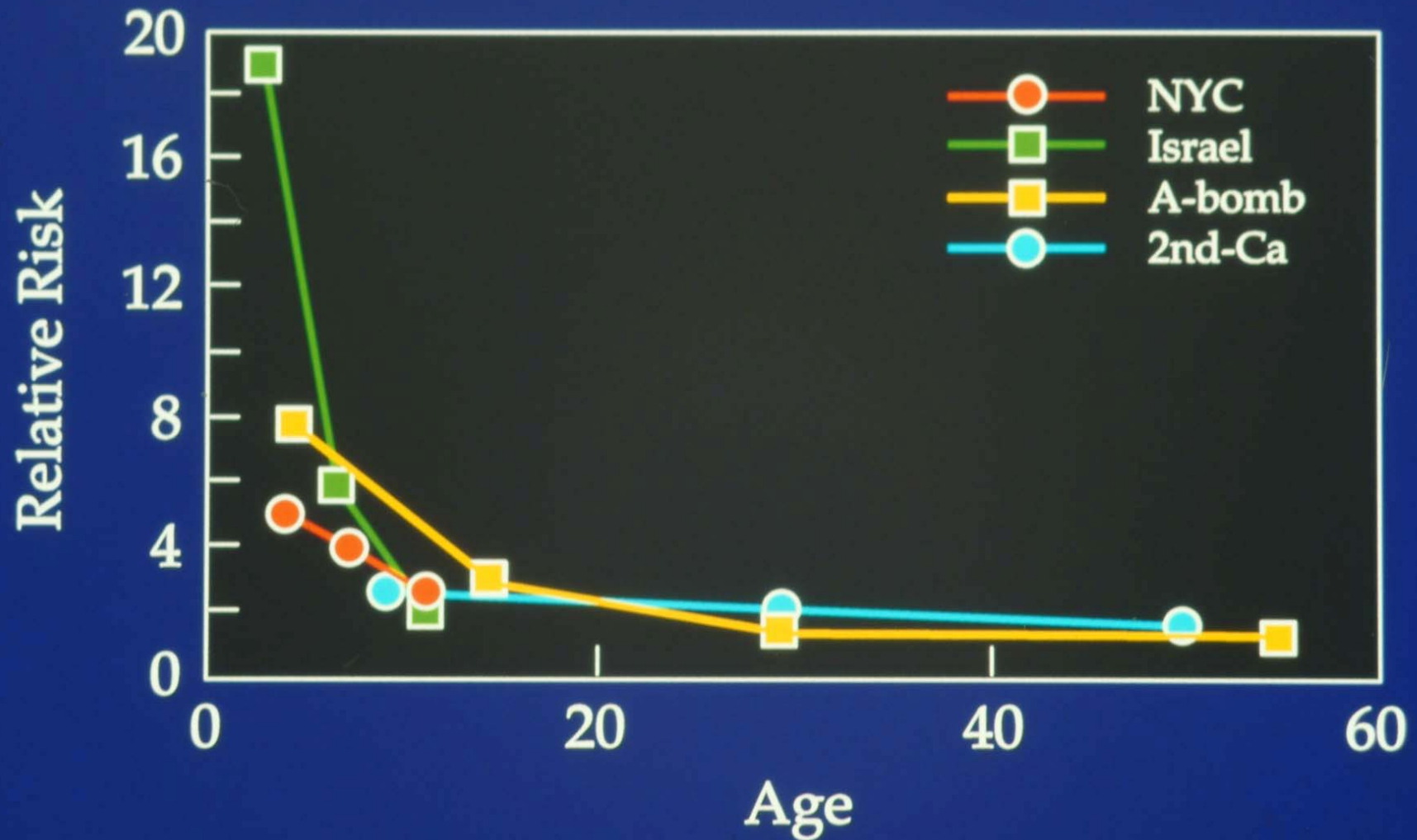


Age at Irradiation

Pooled Thyroid Cancer



BCC Risk by Age at Irradiation



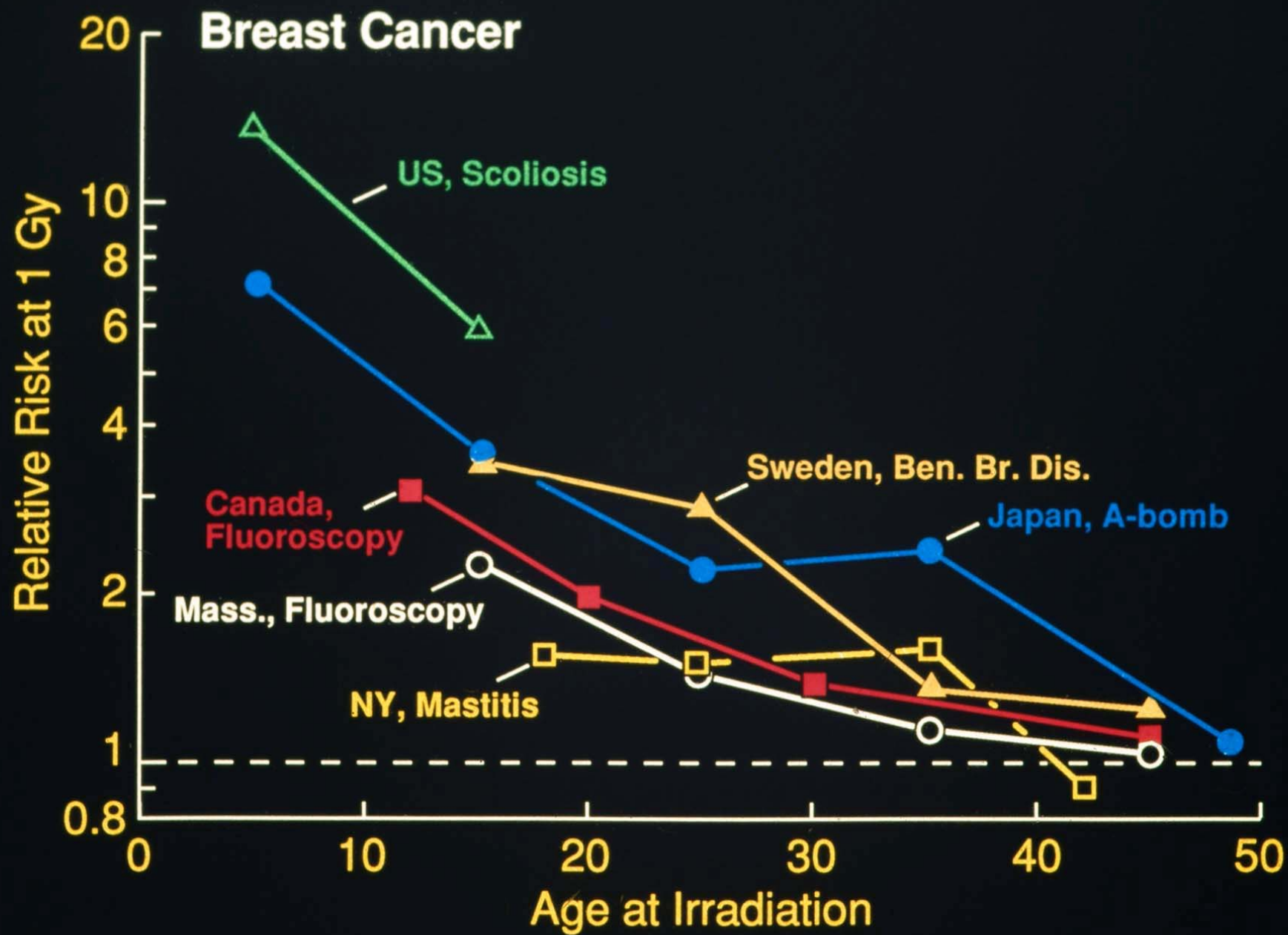
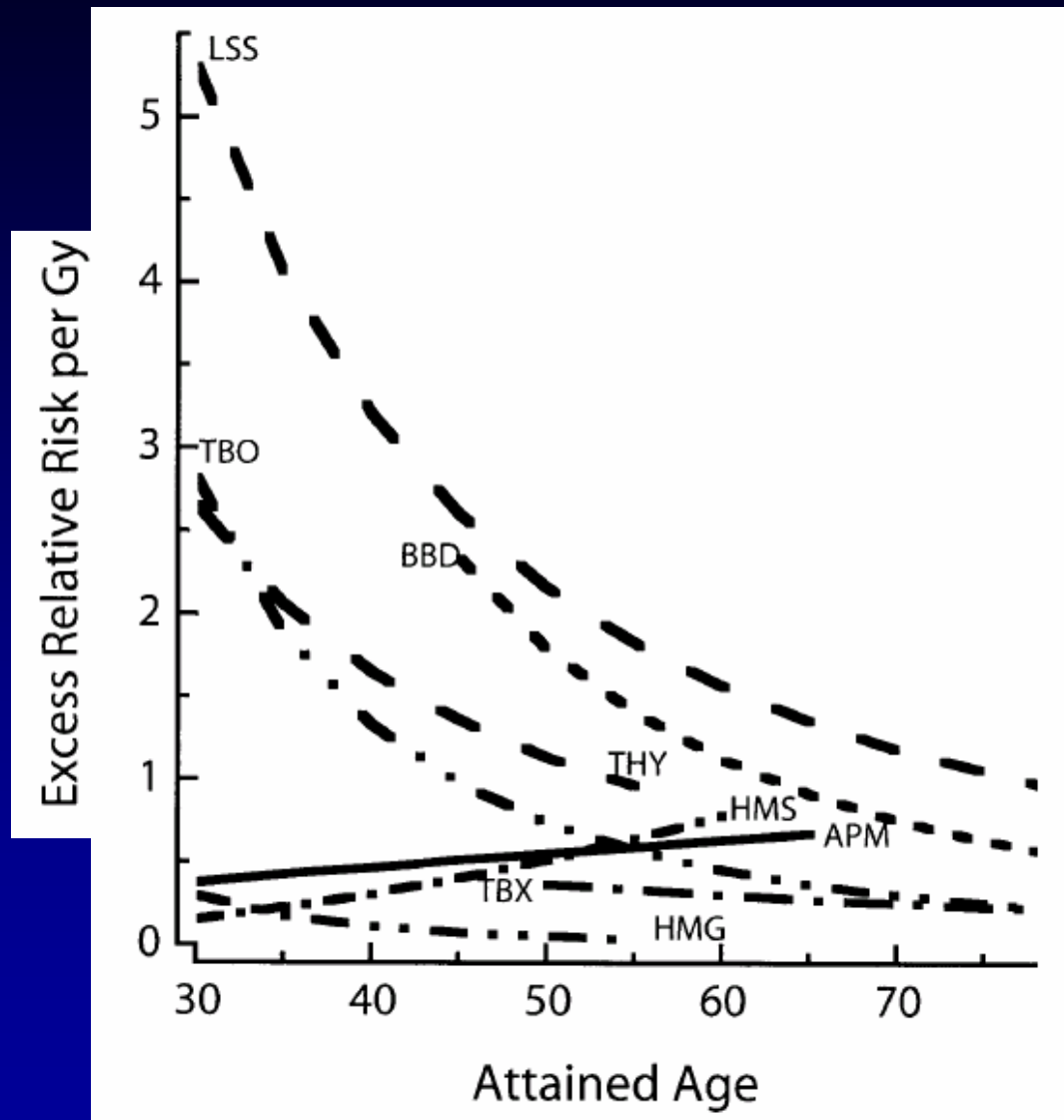
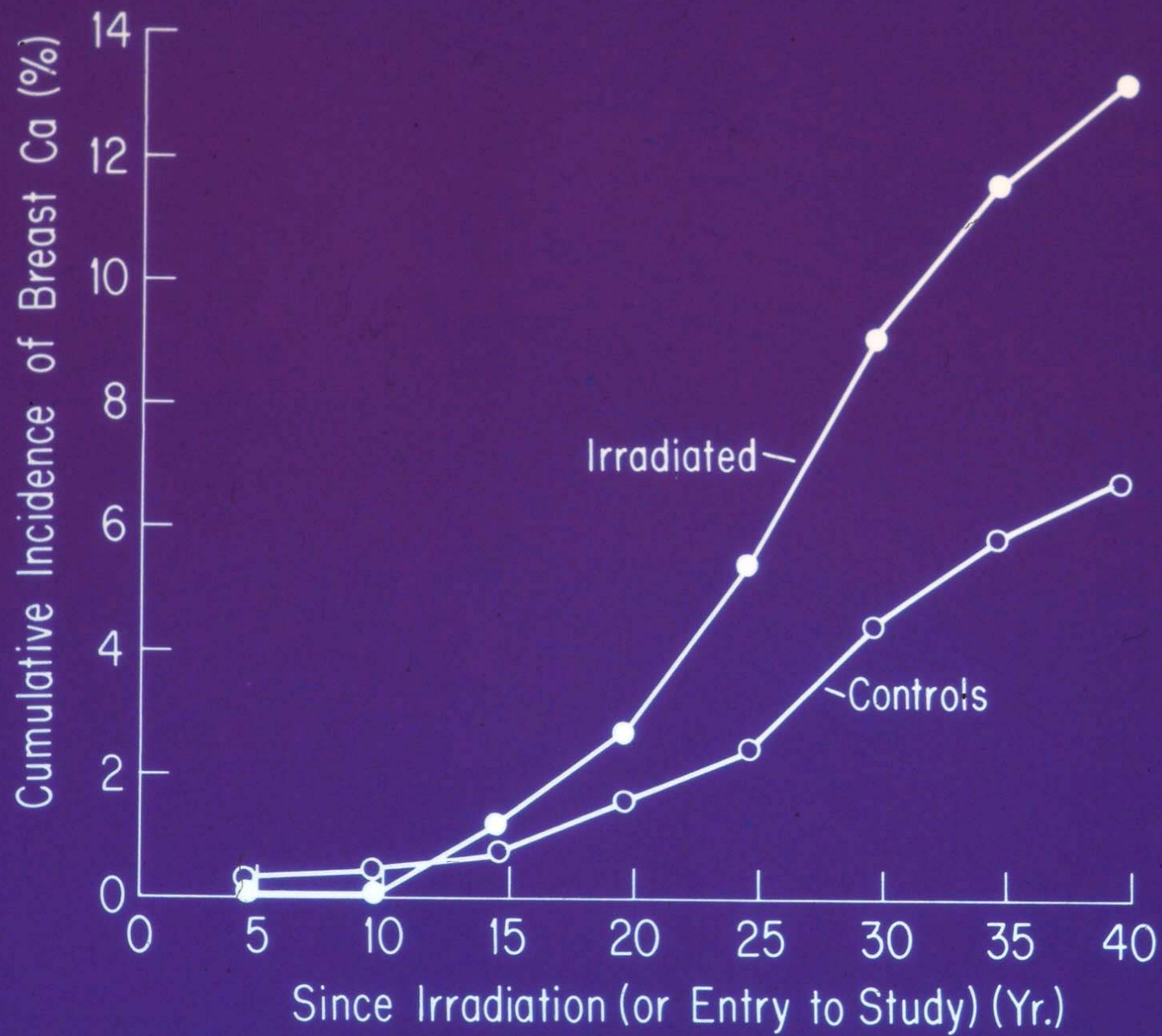


Fig 3B

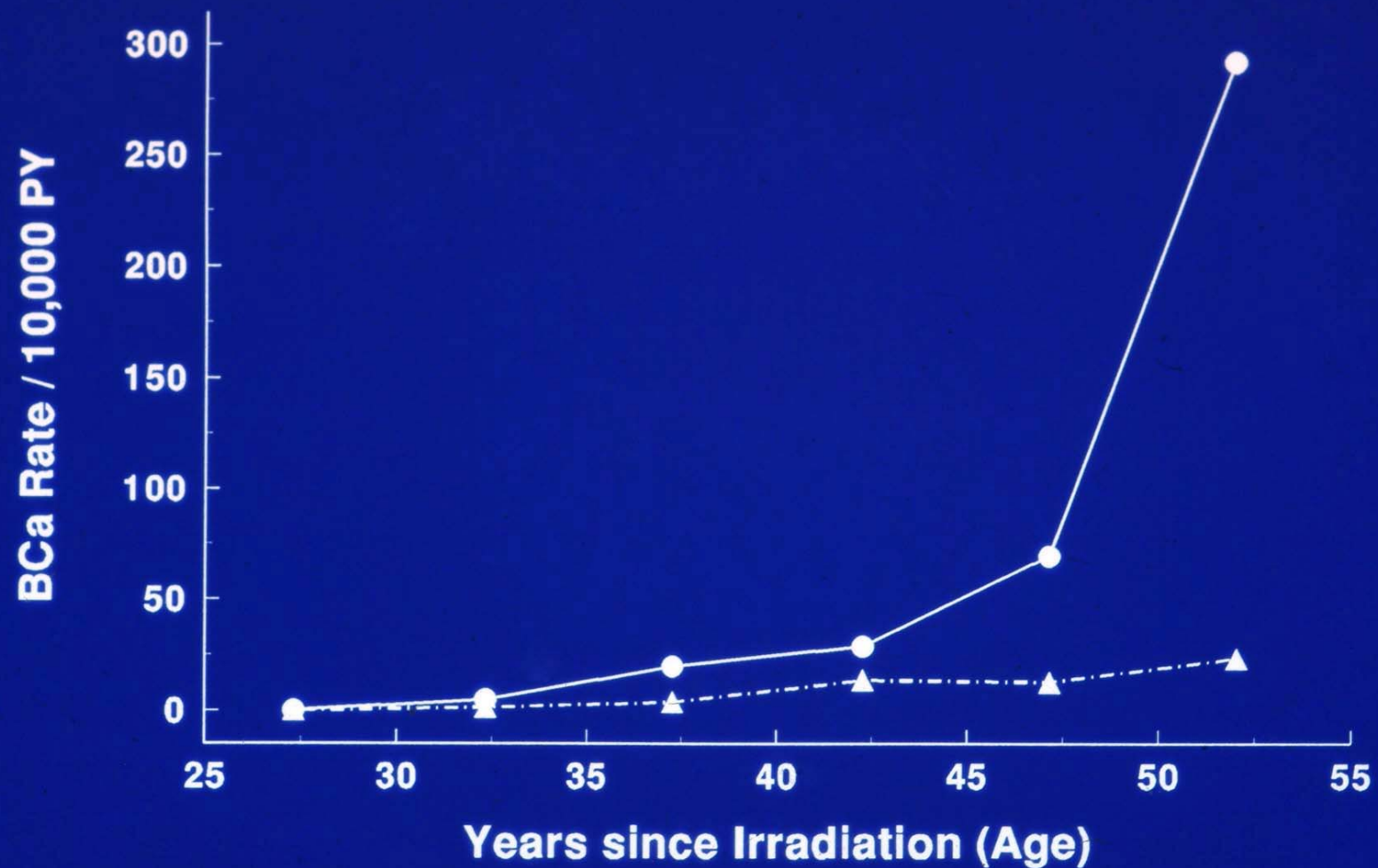


Preston et al, Radiation Research 158:227, 2002.

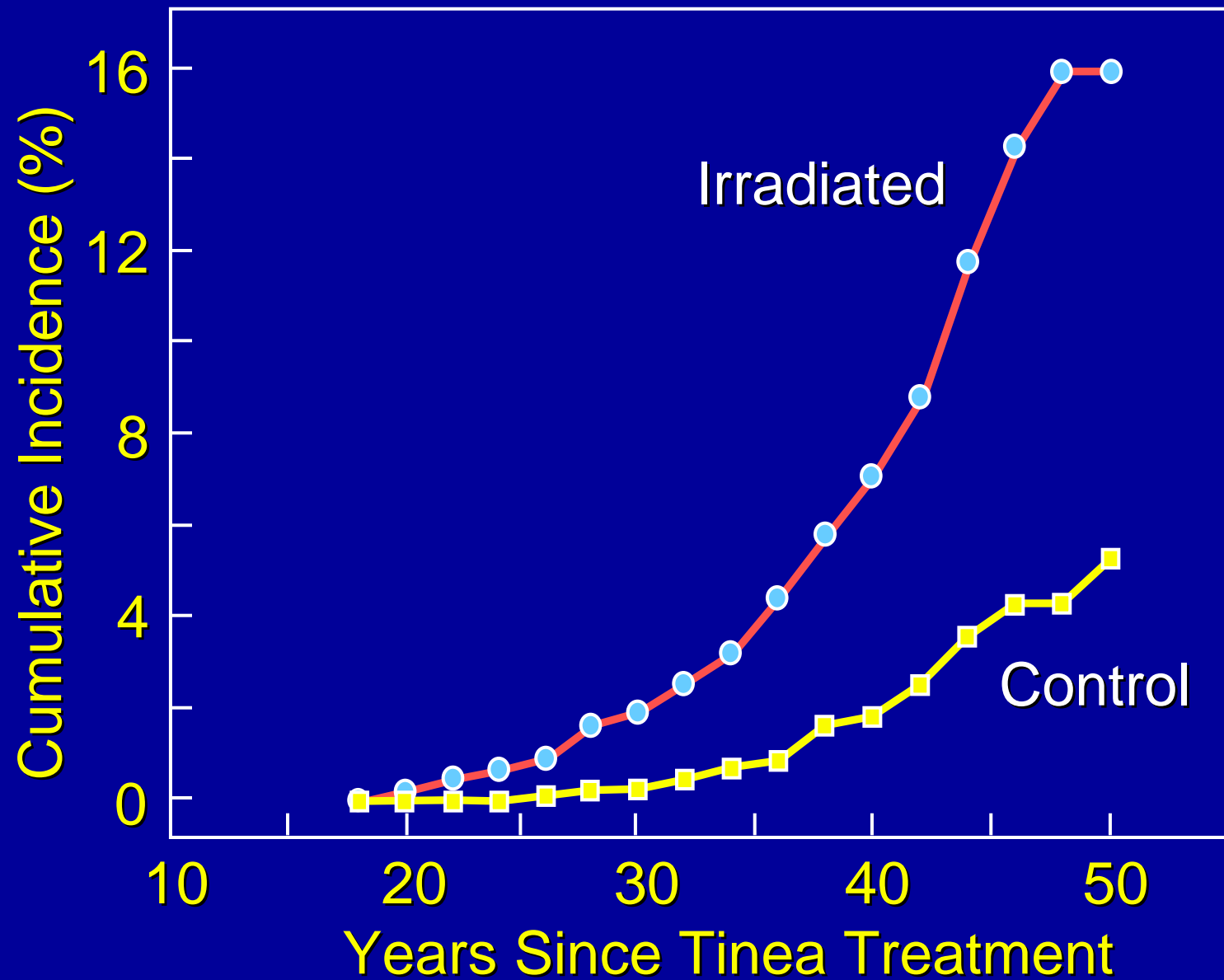
Latency Period for Radiation-Induced Cancer



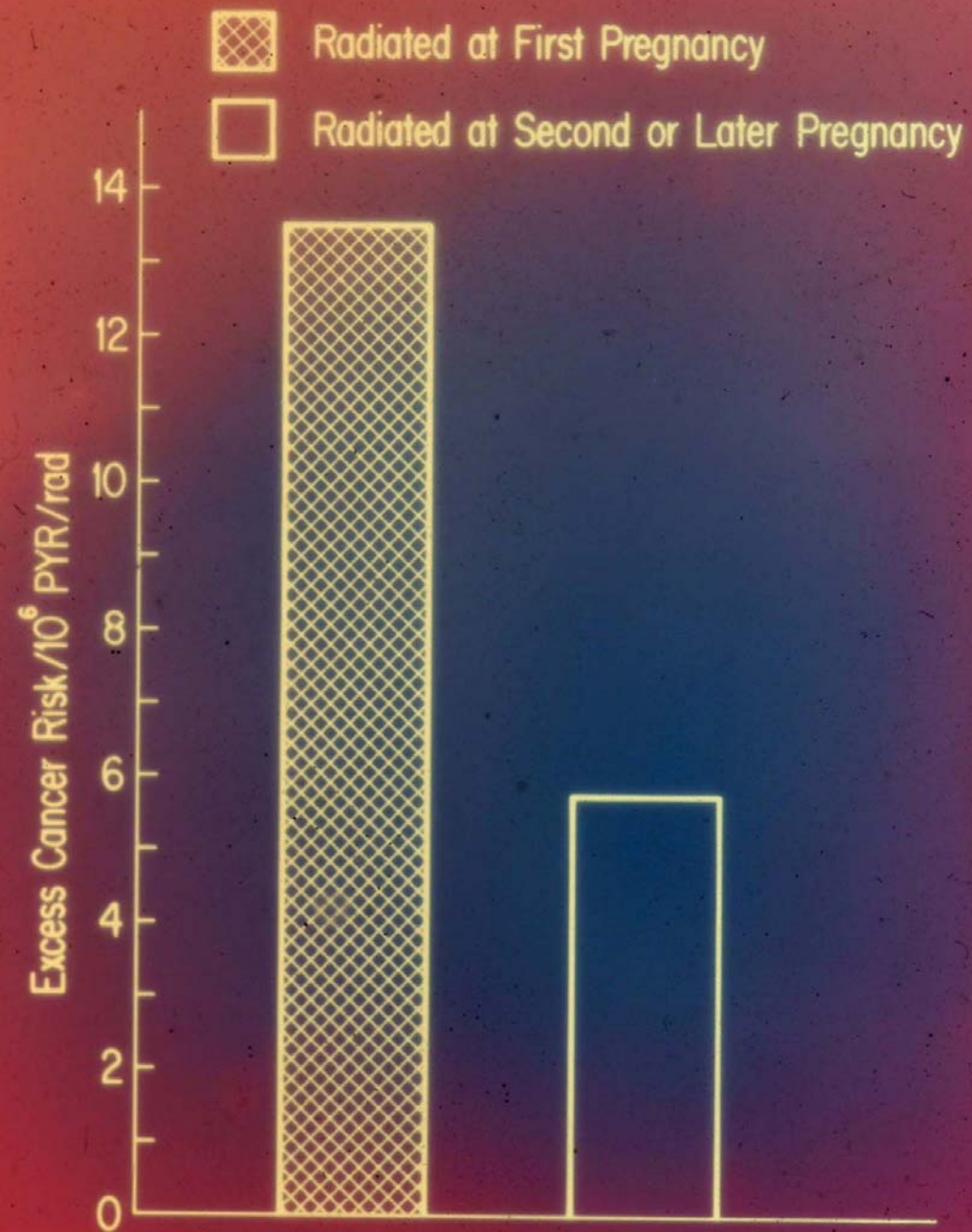
Breast Cancer by Time since Irradiation (Thymus Study)



Skin Cancer: Cumulative Incidence



Modifiers of Radiation Risk



Joint Effects of Ionizing and UV Radiation Exposure on Skin Cancer Risk

- New York tinea study: 90 excess cases in $\frac{3}{4}$ who are whites; 3 excess cases in $\frac{1}{4}$ who are African-American
- A-bomb study: Relative risk higher for UVR-shielded skin than for UVR-exposed skin (head, hands)
- Israel tinea study: Relative risk 2x as high for scalp as for face-neck (but skin dose also higher on scalp)

UVR Exposure, Susceptibility Factors and Skin Cancer in Irradiated Group

- Variables estimating chronic sun exposure at ages 15-20 or in past 5 years: all null or in negative direction.
- History of >5 severe sunburns: $RR = 2.1$ (95% CI = 1.4-3.3)
- North European ancestry, light skin color, blue eyes & sunburn susceptibility predict skin cancer risk

Susceptibility to Radiation-Induced Skin Cancer

Variable	RR (95% CI)
Light skin color (untanned)	1.7 (1.1-2.5) *
Light skin color (tanned)	1.6 (1.1-2.3)
Northern European ancestry	2.0 (2.3-2.9) *
Sunburn severely	1.7 (1.2-2.4) *
Blue eyes	1.6 (1.1-2.3)

Comparability of Results from Medical Irradiation & Other Radiation Studies

Leukemia (non-CLL) & Radiation Exposure

	Mean Dose	Observed/ Expected	ERR/Sv
A-bomb (Pierce, 1996) (F, 10 yo ATB)	0.24	176 / 98	1.7 (1.2-2.3)
Ankylosing spondylitis (Weiss, 1994)	3.8	39 / 12	0.6 (0.3-0.9)
Peptic ulcer RT (Carr, 2002)	1.6	10 / 7.1	1.5 (<0-7)
Skin hemangioma RT (Furst, 1990)	~0.07	15 / 10.7	4.7 (<0-18)
Diagnostic x-ray (Gunz, 1964)	?	35 / 36	RR=1.0 (0.6-1.5)
Dx x-ray (Stewart, 1962)	?	160 / 136	RR=1.3 (1.0-1.6)
Dx x-ray (Boice, 1991)	?	316 / 230	RR=1.4 (0.9-2.2)
Dx x-ray (Gibson, 1972) – 20+ x-rays	?	69 / 45	RR=1.5 (1.0-2.4)
Dx x-ray (Preston-Martin, 1989) - >10	?	54 / 41	RR=1.3 (1.0-1.7)

Studies of Ovarian Cancer & Radiation: All Null/Negative Except LSS Study: **LSS Incidence, ERR/Sv: 0.99 (0.12, 2.34)**

- Cervical cancer RT (Kleinerman) (32)
- Cervical cancer RT (Boice)(32)
- Ra-226 for uterine bleeding (Inskip) (2.3)
- UK x-ray for uterine bleeding (Darby) (5.3)
- US I-131 for hyperthyroid (Ron) (<0.1)
- Canada national dose registry (Sont) (0.002)
- UK registry of radiation workers (Muirhead) (0.006)
- IARC international radiation worker study (Cardis) (<0.04)
- US radiologic techs (Sigurdson) (?)

Radiation-induced Total Solid Tumors after High-dose, Acute Exposures

Study	Mean Dose (mSv)	Obs. / Expec. Ca	% ERR Sv ⁻¹ (95% CI)
A-bomb: mortality (Pierce, 1996)	240	4565 / 4231	40 (31, 51)
A-bomb: incidence (Thompson, 1994)	264	8613 / 7385	63 (52, 74)
²²⁶ Ra implant, uterine bleeding (Inskip, 1993)	~500	1457 / 1096	66 (52, 80)

Radiation-induced Total Solid Tumors after Low-dose or Protracted/Fractionated Exposures

Study	Mean Dose (mSv)	Obs. / Expec. Ca	% ERR Sv ⁻¹ (95% CI:)
Multiple fluoroscopic exams (Davis, 1987)	120	173/169	18 (-104, 154)
¹³¹ I for hyperthyroidism (Holm, 1991)	~60	1543/1456	100 (13, 190)
Chinese medical x-ray workers (Wang, 2002)	~240	836/702	80 (46, 114)
IARC pooled study (Cardis, 1995)	40	1596/1602	-10 (-40, 30)
Techa River (Kossenko, 1994)	~130	774/589	235 (160,320)

Radiation Dose & Breast Cancer Mortality in the Canadian Multiple Fluoroscopy Study and Japanese Atomic Bomb Study

(Howe, *Radiat Res* 145:694, 1996)

	Multiple Fluoroscopy		Atomic Bomb	
Breast Dose (mSv)	# BCa	RR (95% CI:)	# BCa	RR (95% CI:)
<10	332	1.0 (ref.)	57	1.0 (ref.)
10-	120	1.09 (0.88-1.34)	68	1.05 (0.73-1.50)
500-	73	1.11 (0.86-1.43)	15	2.14 (1.19-3.83)
1000-	75	1.38 (1.07-1.77)	11	2.47 (1.29-4.73)
2000-	27	1.69 (1.14-2.51)		
3000-	20	2.36 (1.49-3.75)		
4000-	18	1.92 (1.08-3.42)		
7000-	7	7.6 (3.5-16)		
10,000+	9	27.9 (14-57)		

Radiation Dose & Breast Cancer Mortality in the Canadian Multiple Fluoroscopy Study and Japanese Atomic Bomb Study

- Once age at risk is controlled for, the dose-response coefficients (ERR/Sv) for Hiroshima (0.6), Nagasaki (1.9) & non-Nova Scotia Canada (1.2) were similar (not heterogeneous), but the risk estimate in Nova Scotia (10.3) was greater than the others.
- Conclusion: Dose fractionation does not appear to confer less risk for breast cancer than acute exposure.

Radiation Dose & Lung Cancer Risk for Canadian Multiple Fluoroscopy Study and Japanese Atomic Bomb Study

	Multiple Fluoroscopy		Atomic Bomb	
Lung Dose (mSv)	# Lung Ca	RR (95% CI:)	# Lung Ca	RR (95% CI:)
<10	723	1.0	248	1.0
10-499	180	0.87 (0.7-1.0)	290	1.26 (1.1-1.5)
500-999	92	0.82 (0.7-1.0)	38	1.45 (1.0-2.1)
1000-1999	114	0.94 (0.8-1.2)	30	1.93 (1.3-2.9)
2000-2999	41	1.09 (0.8-1.5)	10	2.65 (1.5-4.7)
3000+	28	1.04 (0.7-1.5)	3	--

Howe G, *Radiat. Res.* 1995; 142:295

Radiation Dose & Lung Cancer Risk for Canadian Multiple Fluoroscopy Study and Japanese Atomic Bomb Study

- Question: Is it the case that radiation fractionation protects against excess lung cancer risk? Or is there another explanation for the findings?

Cancer Risk from In Utero Exposure

Title

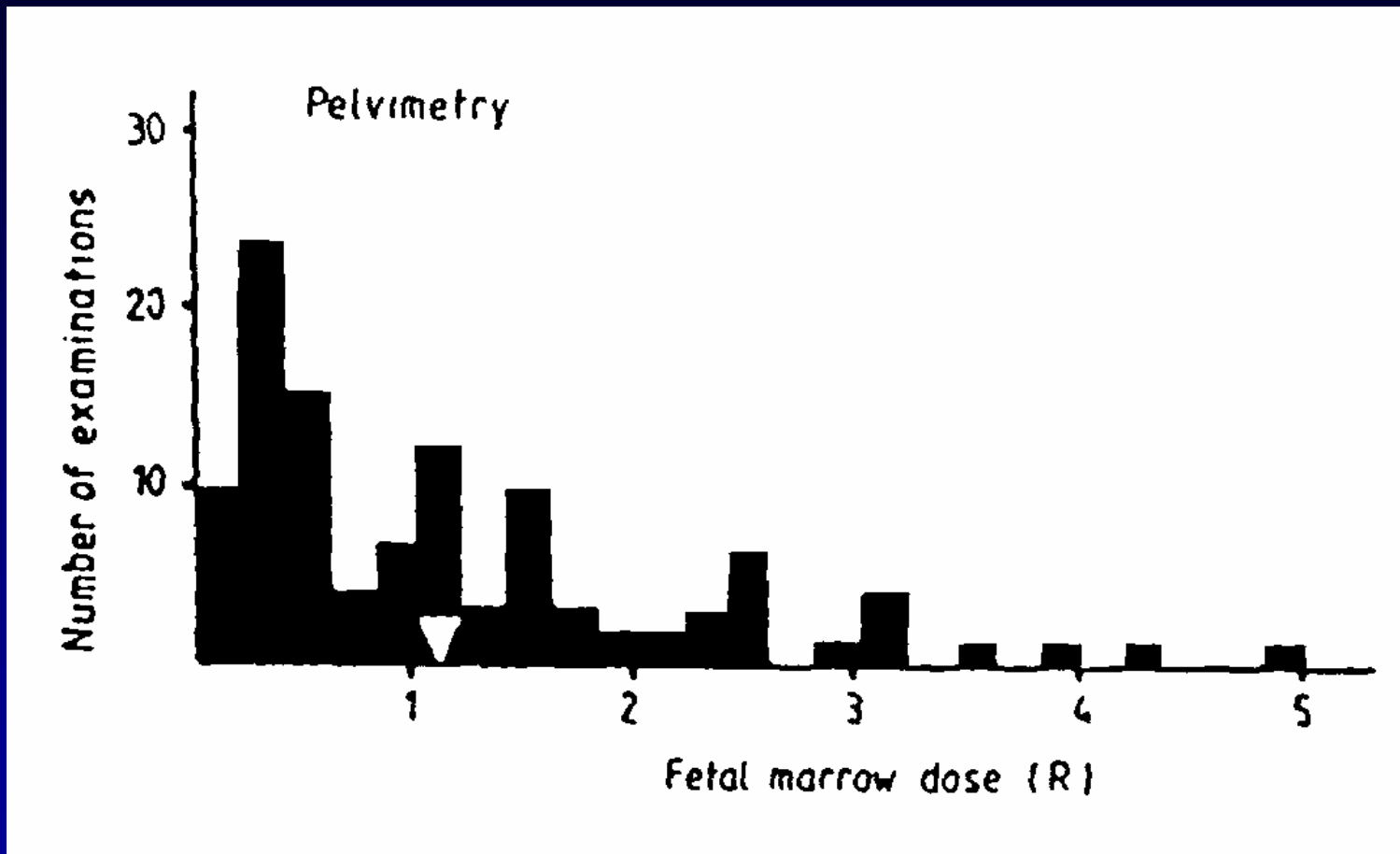


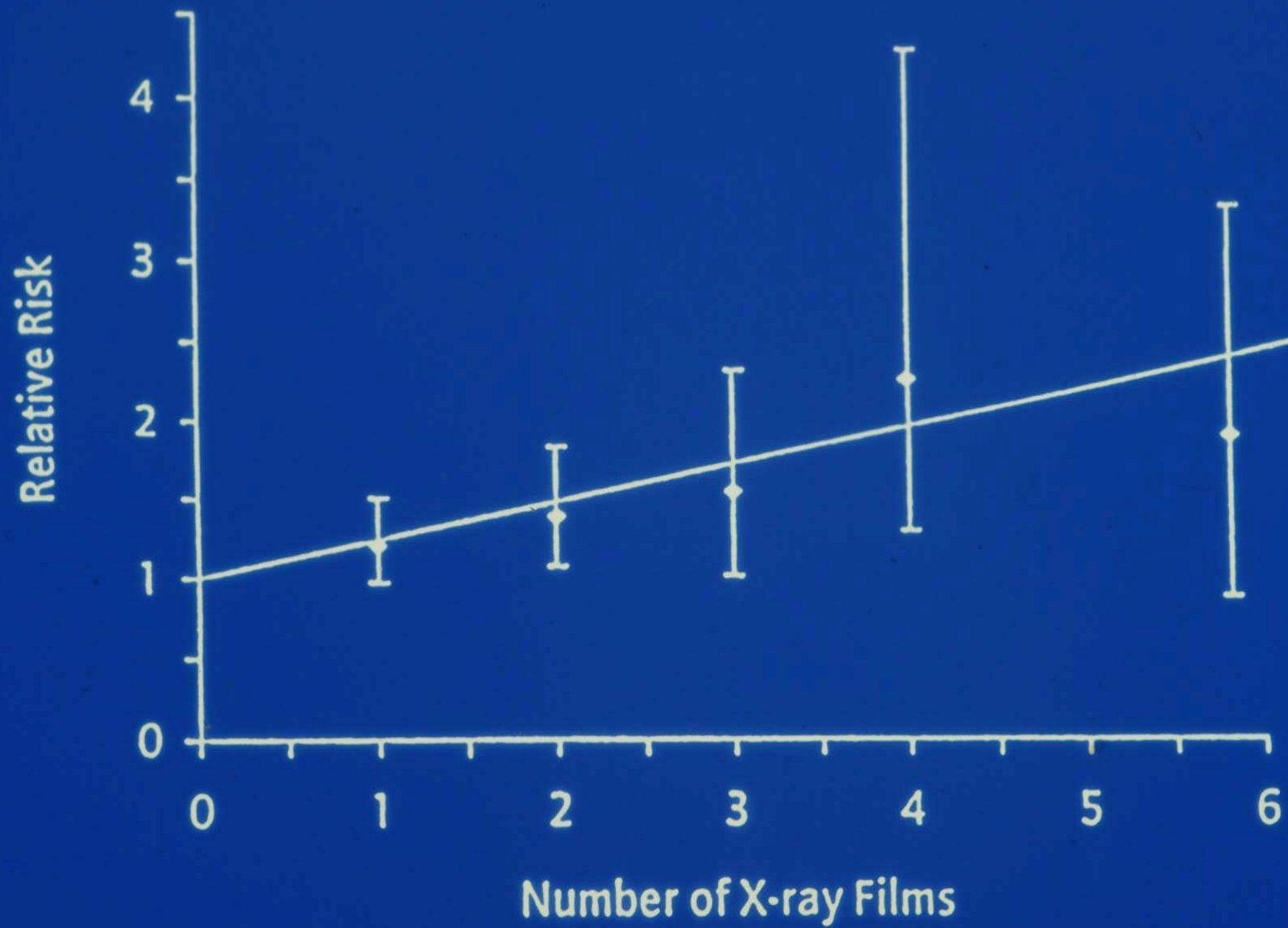
Figure 2. Distribution of fetal bone marrow doses in pelvimetry, based on a nationwide survey in the UK in 1958. The mean value is shown by the inverted white triangle. From: [Mole, 1990]

Oxford Study of Childhood Cancers (OSCC)

- 15,276 childhood cancer deaths, matched 1:1 to live controls (matching on gender, date of birth and being born in the civil district where the case's death occurred)
- 2,182 cases reported to have *in utero* x-ray.
- Exposures: 1944-80
- Died: 1953-81 (ages 0-15)

Effects of In Utero Exposures: Doll-Wakeford (1997) Summary of the Evidence

- Recall bias: a concern, but concern mitigated by Monson study that used hospital records
- No confounding factors have been identified (e.g., similar RRs for twins and singletons)
- Both risk and dose have diminished with chronological time
- Increase in RR with the increase in the number of x-ray exposures



Uncertainty about Magnitude of Effects from Limitations in Studies

- Potential for selection bias, and especially recall bias, in most of the available case-control studies;
- Uncertainties in fetal doses, particularly for obstetric examinations in the early calendar-year eras and for non-obstetric x-ray procedures;
- Cohort studies of medical irradiation: Small numbers of cancers, no radiation effect;
- Finding virtually no excess childhood cancers in those irradiated *in utero* in the Japanese atomic bomb study – only 1 case was observed when ~5-6 expected based on the risk estimate from the OSCC.

OSCC: Selection Bias?

- Only fatal cancers included. Potential for bias increased with calendar time, since case-fatality rates dropped from 70% in 1950-54 to 40% in 1973-77
- Only 66% of case-control pairs were interviewed. Attrition ranged from 20% in early years to 45-50% in later years
- Result: Losses ranged from ~45% in early years (70% decedents x 80% with parent interview) to 75-80% in later years (40% decedents x 50-55% with interview)

OSCC: Information Biases

- A variety of doctors and nurses from local health departments obtained the interview data, apparently without interview training.
- Interviewers were probably aware of case/control status of child.
- Interviewing parents of dead cases but live, healthy controls – differential recall of events?
- Suggestions of Bias: Compared to control mothers, mothers of cases more frequently reported non-abdominal x-rays during pregnancy ($RR=1.17$), and x-rays before marriage ($RR=1.22$) and between marriage and conception ($RR=1.16$).

Combined Relative Risk Estimates of Childhood Cancer from
Medical *In Utero* Irradiation, Case-Control Studies that
Examined both Leukemia and Solid Cancers

Studies Included in Analysis	Leukemia: RR (95% CI)	Solid Cancers: RR (95% CI)
All, including OSCC	1.43 (1.31-1.56)	1.43 (1.27-1.61)
All except OSCC	1.49 (1.24-1.80)	1.25 (1.04-1.52)

Results of Obstetric-Radiation Cohort Studies

Study	# Irrad. Cancers	Total Cancer: RR (95% CI)	Leukemia: RR (95% CI)
Edinburgh/London ⁽¹⁾	9		0.86 (0.4-1.6)
UK national cohort ⁽²⁾	12	1.20 (0.6-2.5)	
Chicago ⁽³⁾	4	1.19 (0.4-4.0)	0.66 (0.1-5.0)
Baltimore ⁽⁴⁾	13	1.05 (0.5-2.1)	1.62 (0.6-4.6)
US Perinatal Project ⁽⁵⁾	7	1.09 (0.5-2.4)	
Rochester, NY ⁽⁶⁾	3		0.92 (0.3-3.1)
Combined studies	48	1.12 (0.7-1.7)	0.98 (0.6-1.6)

(1) Court-Brown 1960; (2) Golding 1990; (3) Griem 1967, Oppenheim 1974; (4) Diamond 1973; (5) Shiono 1980; (6) Murray 1959

Adult Cancer Deaths, Ages 17-46 y, After *In Utero* Exposure – Atomic Bomb Study

# Irrad. Ca	Total Cancer: RR (90% CI)	Leukemia: RR (90% CI)	Solid Cancers: RR (90% CI)
9	3.1 (1.2, 7.0) ¹	~5 (~1, 19), <1 (Dose-resp)	3.4 (1.3, 7.7) ¹

¹ RR at 1 Gy dose, based on a dose-response analysis.

Adapted from: DeLongchamp, 1997

Equivalence of *In Utero* Radiation Risks for All Types of Childhood Cancer?

Type of Malignancy	RR (95% CI)	# Irradiated Cases
OSCC Study {Bithell, 1975}		
Lymphatic leukemia	1.54 (1.34-1.78)	327
Myeloid leukemia	1.47 (1.20-1.81)	134
Lymphoma	1.35 (1.07-1.69)	109
Brain/CNS tumor	1.42 (1.20-1.69)	198
Neuroblastoma	1.46 (1.17-1.83)	108
Wilms' tumor	1.59 (1.25-2.01)	93
Other solid tumors	1.63 (1.33-1.98)	147
NE United States Study {Monson, 1984}		
Leukemia	1.40 (1.11-1.76)	94
Brain/CNS tumor	1.09 (0.75-1.59)	32
Other cancers	1.14 (0.80-1.63)	36

Equivalent *In Utero* Radiation Risks for All Types of Childhood Cancer?

- Childhood radiation exposure causes marked leukemia effect ($\text{ERR/Gy} = 17$) but smaller solid cancer effect ($\text{ERR/Gy} = 2$) in A-bomb study.

For obstetric x-ray case-control studies the risk is equivalent ($\text{ERR/Gy} \cong 40$) for both leukemia & solid cancers.

- Lymphomas are not thought to be radiogenic following postnatal exposure.
- Embryonal tumors (e.g., neuroblastoma, Wilms tumor) originate in early weeks of gestation. >95% of radiation exposures were in last few weeks of gestation.

Boice-Miller Questions About Whether the Association is Causal

- Lingering doubts about information bias
- No excess of childhood cancer in the atomic bomb study (statistically incompatible with OSCC study)
- All major cohort studies are null
- Equal radiation risk for all types of childhood cancer is unexpected, given the variation in tissue radiosensitivities, tissue origins, etc.
- Risk estimates appear greater for *in utero* vs. newborn exposures for solid cancers.
- Twin cohorts have lower childhood cancer risks, despite more frequent x-rays
- Supporting animal evidence is weak
- No evidence of excess cancer seen in children exposed *in utero* to Chernobyl

Is There Cancer Risk from Irradiation in the First Trimester?

- OSCC {Gilman, 1988}: $RR = 2.7$ for the first vs. third trimester after (inadequately) adjusting for dose differences.
- Monson, 1984: $RR = 1.9$ during trimesters 1-2 (but only 10 irradiated cases), and $RR = 1.3$ in trimester 3.
- Japanese atomic bomb: $ERR/Sv = 12.9$ for 1st trimester and 5.0 for 2nd & 3rd trimesters combined.
6 of 10 adult cancer deaths had *in utero* exposure in 1st trimester.